Boyadzhiev L (1990) Liquid pertraction or liquid membranes – state of the art. *Separation Science and Technology* 25: 187.

Boyadzhiev L and Lazarova Z (1994) Liquid membranes (liquid pertraction). In: Noble RD and Stren SA (eds) *Membrane Separation Technology. Principles and Applications*, pp. 283–352. Amsterdam: Elsevier.

Drioli E and Nakagaki M (1986) *Membranes and Membrane Processes*. New York: Plenum.

Ho WSW and Sirkar KK (eds) (1993) *Membrane Handbook*. New York: Van Nostrand Reinhold.

Li NN (1971) Permeation through liquid surfactant membranes. *American Institute of Chemical Engineers Journal* 17: 459.

Noble RD and Douglas Way J (eds) (1996) *Liquid Membranes. Theory and Application*. American Chemical Society Symposium Series no 347. Washington, DC: American Chemistry Society .

Zhang R (ed.) (1984) *Separation Techniques by Liquid Membranes* (in Chinese). Nanchang: Jiangxi Renmin.

Membrane Bioseparations

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Membrane processes are particularly well suited to the separation and purification of biological molecules since they operate at relatively low temperatures and pressures and involve no phase changes or chemical additives. Thus, these processes cause minimal denaturation, deactivation and/or degradation of highly labile biological cells or macromolecules. Although essentially all membrane processes (**Figure 1**) have been used for bioseparations, the greatest interest has been in the application of the pressure-driven processes of ultrafiltration (UF) and microfiltration (MF). Ultrafiltration membranes have pore sizes between 1 and 50 nm and are used for protein concentration, buffer exchange, desalting, clarification of antibiotics and virus clearance. There is also growing interest in the use of ultrafiltration for protein purification using high performance tangential flow filtration (HPTFF). Microfiltration membranes have a pore size between 0.05 and 10 μm and are thus used for initial clarification of protein solutions, cell harvesting and sterile filtration. In addition, ultrafiltration and microfiltration of blood are used for the treatment of a variety of metabolic and immunological disorders.

The development of membrane processes for bioseparations is very similar to the design of membrane systems for nonbiological applications. However, there are some important differences including:

1. increased concerns about deactivation or denaturation of biological molecules and cells
2. very high value (on a per unit mass basis) of most biological products (particularly recombinant therapeutic proteins)
3. tendency of biological macromolecules and cells to cause significant fouling of both ultrafiltration and microfiltration membranes
4. critical importance of validation and integrity testing in bioprocessing applications

This article provides a brief review of the historical development of membrane systems for bioseparations. This is followed by a general discussion of the

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	Microfiltration	Virus filtration	HPTFF	Ultrafiltration	Nanofiltration	Reverse osmosis
Components retained by membrane	Intact cells Cell debris Bacteria	Viruses	Proteins	Proteins	Nucleic acids Antibiotics	Sugars Salts
	Membrane					
Components passed through membrane	Colloids Viruses Proteins Nucleic acids Sugars Salts	Proteins Nucleic acids Sugars Salts	Proteins Nucleic acids Sugars Salts	Nucleic acids Surfactants Sugars Salts	Salts Water	Water

Figure 1 Classification of pressure-driven membrane processes showing typical bioprocessing applications.

underlying principles governing the design of ultrafiltration and microfiltration systems, with particular emphasis on those factors that are most significant for bioseparations. The reader is referred to the Encyclopedia articles on Membrane Separations – Microfiltration and Membrane Separations – Ultrafiltration for more detailed discussions of these membrane technologies.

Historical Development

The first mention of the process now known as ultrafiltration appears to have been in an 1856 study by Schmidt on the filtration of protein and gum arabic through animal membranes. Thus, the idea of using ultrafiltration for bioseparations dates back well over 100 years. Bechhold coined the term ultrafiltration in 1906 during a systematic study of the behaviour of different pore size collodion membranes made by impregnating filter paper with acetic acid and cellulose nitrate. Zsigmondy obtained one of the first patents in membrane technology in 1922 for the preparation of flat collodion membranes from ether–alcohol solutions. The first efforts to develop microporous membranes in the USA were motivated by the need for rapid detection and analysis of biological warfare agents. This technology was subsequently transferred to the Lovell Chemical Company, which ultimately led to the establishment of Millipore Corporation.

The early historical development of ultrafiltration and microfiltration is described in an excellent review article by Ferry in 1936. The primary applications of membrane technology in the early 1900s were for a variety of biological, analytical and bacteriological assays. Ferry also described the use of membranes for enzyme concentration, analysis of bacteriophages and viruses, blood ultrafiltration to prepare cell- and protein-free ultrafiltrates, sterile filtration of biological solutions and the partial separation of albumin from globulins in blood serum. All of these bioseparations remain areas of active commercial interest even today.

Although many of the potential uses of membrane systems in bioprocessing were identified well over 60 years ago, the collodion (cellulose nitrate) membranes available at that time had inadequate chemical, mechanical and mass transport properties for the effective use of ultrafiltration on an industrial scale. The key breakthrough was the development of the asymmetric cellulose acetate reverse osmosis membrane by Loeb and Sourirajan in the early 1960s and the subsequent extension of this technique to produce asymmetric ultrafiltration membranes. These asymmetric membranes have a very thin skin (approximately 0.5 μm thick), which provides the membrane with its selectivity, and a more macroporous substructure, which provides the required mechanical and structural integrity. The thin skin results in much higher permeation rates than are obtainable with homogeneous membranes, significantly reducing the required membrane area and/or process time.

Ultrafiltration is now used throughout the downstream separation process for the purification of therapeutic recombinant proteins, blood components, natural protein products and industrial enzymes. Specific applications include protein concentration (i.e. volume reduction), desalting and buffer exchange, all of which are used to condition the product prior to, or immediately after, other separation processes or as part of the final product formulation. In addition, ultrafiltration is used extensively for the clarification of antibiotics, amino acids and other small biological molecules. Recent work has demonstrated that ultrafiltration membranes are also capable of effecting protein–protein separations using a process known as HPTFF. Microfiltration membranes are used for cell harvesting, initial clarification of cell culture media and fermentation broths, and for sterile filtration of products that are directly added to pre-sterilized containers. Sterile filters are also used to remove bacteria and particles from feedstock solutions and to reduce the overall bioburden in processes where the product will be subjected to a terminal sterilization step. Virus removal membranes are used as part of the overall viral clearance required for the production of therapeutic proteins and blood products. Virus filters can also provide a protective barrier for bioreactors through the filtration of media and buffer solutions.

Ultrafiltration and Microfiltration Principles

Membrane Selection

Membrane selection should start with the choice of a high quality vendor since robustness, reliability and reproducibility of manufacturing operations are of paramount importance in most bioprocessing applications. Consistent membrane and device characteristics can be as important to product quality, yield and economics as the inherent differences between various membranes and devices. Cellulosic membranes are attractive for many bioprocessing applications because of their low protein adsorption and low fouling characteristics. Synthetic polymers (e.g. polysulfone and polyvinylidene fluoride) are also attractive due to their greater chemical and mechanical stability. These polymers are often surface-treated to

render them more hydrophilic to reduce protein adsorption and fouling. Membranes used for sterile filtration must be steam-sterilizable, have minimal particle shedding, low extractables and must pass United States Pharmacopoeia (USP) Class VI toxicity testing.

Most manufacturers rate ultrafiltration membranes by their nominal molecular weight cutoff, which is defined as the molecular weight of a solute with a particular retention coefficient:

$$R = 1 - C_{\text{filtrate}}/C_{\text{feed}} \quad [1]$$

where C_{filtrate} and C_{feed} are the solute concentrations in the filtrate solution and feed stream, respectively. Data are typically obtained with a range of model proteins or with polydisperse dextrans. Unfortunately, the procedures used for assigning molecular weight cutoffs, including the choice of solutes, the specific buffer and flow conditions, and the chosen retention value (usually $R = 0.9$) vary widely throughout the industry. In addition, ultrafiltration systems used in bioprocessing generally require protein retention of at least 99%, and often as high as 99.9%, to minimize loss of high value products through the membrane. Data obtained with solutes having $R = 0.9$ are often of little value in determining whether a given membrane can provide these high levels of protein retention due to differences in the details of the pore size distributions.

Microfiltration membranes are typically rated by their pore size or their particle retention characteristics using the log reduction value (LRV), defined as the logarithm (base 10) of the ratio of the particle, cell or virus concentration in the feed to that in the filtrate solution. Sterilizing-grade (0.2 μm pore size) filters are currently defined by the Health Industry Manufacturing Association (HIMA) as a filter which produces a sterile filtrate when challenged by 10^7 colony-forming units of *Brevundimonas diminuta* (formerly classified as *Pseudomonas diminuta*) per cm^2 of membrane area. This challenge uses the smallest bacteria at a concentration that exposes essentially every pore to the microorganisms. Sterile filters are often thought of as operating via a purely size-based (sieving) mechanism, although bacteria can also be removed by adsorption on to the membrane surface.

The chemical compatibility of the membrane needs to be verified with the feed, regeneration chemicals and storage solutions. Sodium hypochlorite (NaOCl) is used most extensively for chemical disinfection of membrane systems in bioprocessing applications. Many membrane systems are designed for steam-in-place (SIP) sterilization, with the entire unit exposed to flowing steam as part of the completely assembled filtration system. Minimum requirements for an effective steam sterilization are 15 min exposure to steam at 121°C and 1 atm pressure. Polysulfone membranes tend to have broader chemical and thermal stability than cellulosic membranes but also require harsher chemical treatment for regeneration due to their greater fouling characteristics. Inorganic (ceramic) membranes have the greatest chemical compatibility, but they are much more expensive than polymeric membranes. The mechanical strength of the membrane is important since reverse-pressure spikes can cause membrane delamination and catastrophic yield loss.

Module Design

Dead-end, or normal-flow, filtration (**Figure 2A**) is used primarily for laboratory-scale separations and for systems in which the retained species are present at very low concentration. For example, dead-end microfiltration cartridges are used extensively for sterile filtration since the retained bacteria are present at very low concentration. Similar modules can be employed for virus removal applications. Almost all large scale commercial ultrafiltration devices use tangential flow filtration, also referred to as a cross-flow configuration, in which the feed flow is parallel to the membrane and thus perpendicular to the filtrate flow (Figure 2B). This allows retained species to be swept along the membrane surface and out of the device exit, significantly increasing the process flux compared to that obtained with dead-end operation.

A number of tangential flow modules have been developed for ultrafiltration and microfiltration

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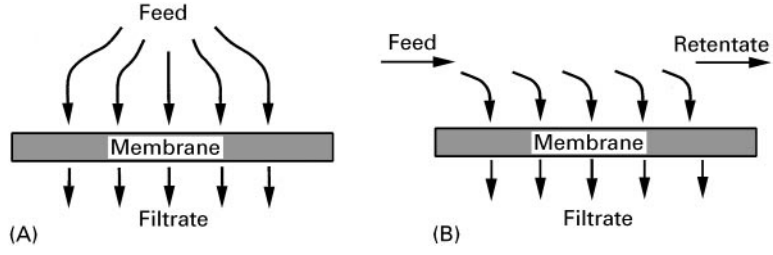

Figure 2 Comparison of (A) dead-end and (B) cross-flow configurations.

Table 1 Comparison of different module configurations

Module configuration	*Channel spacing (cm)*	*Packing density ($m^2\ m^{-3}$)*	*Energy costs (pumping)*	*Particulate plugging*	*Ease of cleaning*
Flat sheet	0.03–0.1	300	Moderate	Moderate	Good
Hollow fibre	0.02–0.25	1200	Low	High	Fair
Tubular	1.0–2.5	60	High	Low	Excellent
Spiral wound	0.03–0.1	600	Low	Very high	Poor to fair

processes, differing primarily in the size and shape of the feed and filtrate flow channels. **Table 1** provides a general summary of the physical characteristics of the most common modules. Detailed descriptions of these modules are available elsewhere.

The small channel spacing in flat-sheet, hollow-fibre and spiral-wound modules provides high membrane-packing densities. In addition, these modules have low hold-up volumes, which facilitates the recovery of high value products. The screens used to define the flow path in spiral-wound modules and many flat-sheet cassettes are susceptible to particle plugging and this may make cleaning more difficult. Hollow-fibre membranes are self-supporting, so they can often be cleaned by simple backflushing. The large-bore tubular membranes can be cleaned by both physical and chemical methods. However, these modules operate in the turbulent flow regime which can cause cell lysis, protein denaturation or aggregation. A variety of enhanced mass transfer modules which exploit flow instabilities have also been developed for bioprocessing applications. Rotating cylinder modules which induce Taylor vortices have very high mass transfer rates, although there are concerns about the moving parts. Another attractive approach is to use helically coiled hollow fibres wrapped around a central core to induce Dean vortices.

Process Configurations

Protein concentration can be carried out using either batch or fed-batch operation (**Figure 3**). In a batch process, the entire feed volume is contained within the recycle tank. Tank design is critically important to ensure adequate mixing while avoiding air entrainment and excessive foaming. Batch operation uses a minimum of hardware and allows simple manual or automatic control. The flux rates are also higher in batch processes since the bulk concentration follows a more dilute path in going from initial to final concentration. Disadvantages of the batch configuration include less flexibility in using the same system for multiple processes, greater difficulty in designing a well-mixed system, and difficulties in obtaining high concentration factors.

The fed-batch configuration utilizes an additional tank to feed into the recycle tank (Figure 3). Fed-batch configurations are commonly used to obtain high concentration factors and to provide well-mixed, low-hold-up, retentate reservoirs. These systems also provide flexibility for use in multiple processes. The disadvantages of the fed-batch system include greater process time and greater number of passes of the retentate through the pumps and valves in the recycle line. The latter can lead to excessive cell lysis, protein denaturation or aggregation.

Diafiltration is commonly used for buffer exchange (for products in the retentate) and to enhance yield (for products in the filtrate). The diafiltration system looks similar to the fed-batch configuration shown in Figure 3 except that the feed tank contains a buffer solution which is added to the recycle tank. The most common approach is constant retentate volume diafiltration in which the buffer is added at the same rate as filtrate removed.

The yield and purification obtained in ultrafiltration and microfiltration processes can be evaluated from simple mass balances on the product and impurity assuming constant rejection coefficients. The final product concentration (C_F) at the end of a batch concentration process is given as:

$$\left(\frac{C_F}{C_0}\right) = \left(\frac{V_0}{V_F}\right)^{1-S} \qquad [2]$$

where V_F is the final retentate volume, V_0 is the initial retentate volume and S is the product sieving coefficient (equal to one minus the rejection coefficient). The analogous expression for a fed-batch process is:

$$\frac{C_F}{C_0} = \frac{1}{S} + \left(1 - \frac{1}{S}\right)\exp\left[-S\left(\frac{V_0}{V_F} - 1\right)\right] \qquad [3]$$

The final concentration after a constant retentate volume diafiltration is:

$$\frac{C_F}{C_0} = \exp(-SN) \qquad [4]$$

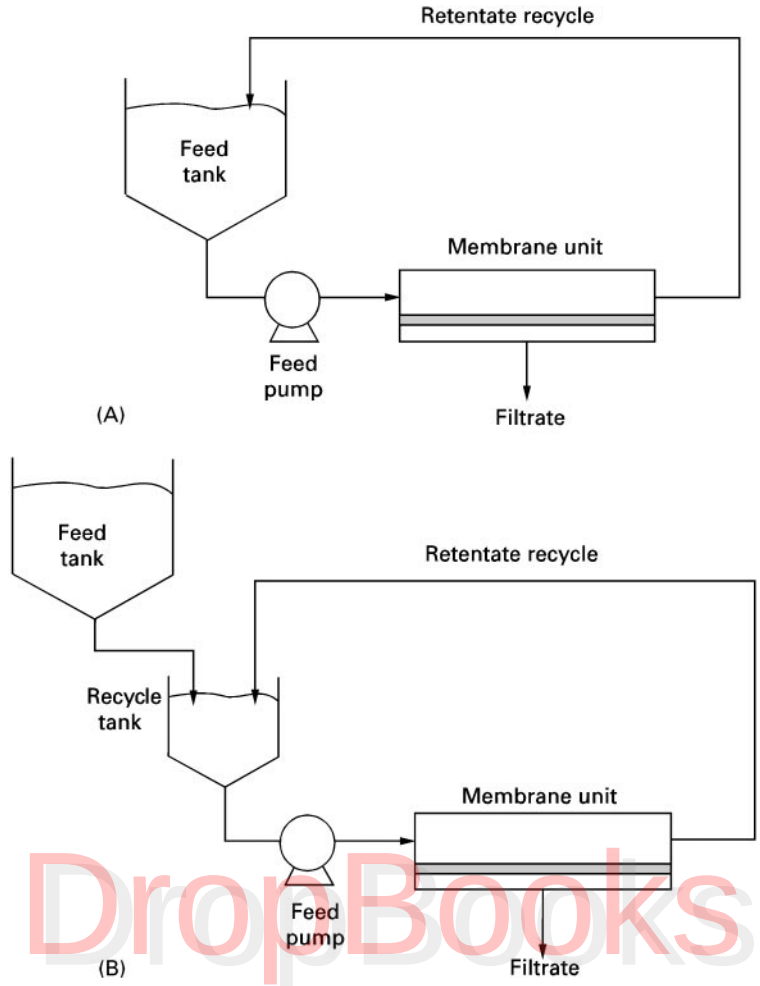

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Figure 3 Comparison of (A) batch and (B) fed-batch processes for protein concentration.

where the number of diavolumes (N) is given by:

$$N = V_D/V \qquad [5]$$

where V_D is the diafiltration buffer volume. Even very small sieving coefficients may result in substantial product loss when a large number of diavolumes are required in diafiltration processes. For example, a diafiltration process with a product sieving coefficient of $S = 0.01$ will result in a 10% product loss during a 10 diavolume buffer exchange.

Concentration Polarization

One of the critical factors determining the overall performance of tangential flow filtration devices is the rate of solute/particle transport in the bulk solution adjacent to the membrane. The filtrate flow causes an accumulation of partially (or completely) retained components at the upstream surface of the membrane, a phenomenon referred to as concentration polarization. The concentration thus varies from its maximum value at the membrane surface (C_w) to its bulk value (C_b) over the thickness of the concentration boundary layer (δ). Most analyses of concentration polarization have employed the simple stagnant film model in which:

$$J = k \ln\left(\frac{C_w - C_f}{C_b - C_f}\right) \qquad [6]$$

where J is the filtrate flux (typically in L m^{-2} h^{-1}) and k is the solute mass transfer coefficient in the particular membrane device. The accumulation of particles/solutes at the membrane surface increases the overall resistance to filtrate flow through the formation of a particle cake or gel layer and it can reduce the effective pressure driving force through the osmotic pressure of the retained solutes. At high transmembrane pressures, the wall concentration approaches a maximum value determined by the close-packed concentration of the particles or cells, the

protein solubility limit or the concentration at which the osmotic pressure of the retained solutes is essentially equal to the applied transmembrane pressure. The net result is that the flux attains a nearly constant pressure-independent value that increases with decreasing bulk concentration and increasing feed flow rate. The dependence on feed flow rate is determined by the module characteristics: approximately 1/3 power for laminar flow in hollow fibres and open channels, 1/2 power for screened channels, and 0.8 power for turbulent flow in tubular modules. The dependence on feed flow rate for cellular suspensions is typically greater than that for protein solutions due to shear-induced particle diffusion and inertial lift effects.

Process Control

Ultrafiltration and microfiltration processes have traditionally been performed at constant transmembrane pressure. Constant-pressure processes are very simple to control. The feed rate is ramped up to the set point and the retentate valve is then partially closed to obtain the desired transmembrane pressure. The transmembrane pressure should be gradually increased to minimize fouling. In some applications it may not be possible to maintain constant transmembrane pressure without severe reductions in filtrate flux over the course of the process due to membrane fouling. This is particularly true for cell microfiltration where the high initial flux leads to very rapid deposition of cells and cell debris on the membrane surface. Several studies have shown that higher overall throughput can often be obtained in these applications by operating at constant filtrate flux. The flux is controlled by regulating the retentate pressure control valve or by using a pump on the filtrate line.

A third method of process control that is very attractive for bioprocessing applications is to vary the filtrate flux so that the wall concentration of retained species (evaluated from eqn [6]) remains constant during the process. Control is performed using a proportional-integral-derivative (PID) loop that measures flux and controls the transmembrane pressure or filtrate flow rate to maintain a constant wall concentration throughout the process. The benefits of constant C_w control are that product yield is maximized, product quality is ensured, membrane area is minimized and process time is consistent and independent of variations in membrane permeability.

High Performance Tangential Flow Filtration

Ultrafiltration and microfiltration have traditionally been limited to separating species that differ in size by at least 10-fold. In contrast, HPTFF enables the separation of solutes without limit to their relative size. HPTFF is able to obtain the high selectivity required for effective protein purification by exploiting several recent developments. Firstly, HPTFF is operated in the pressure-dependent regime, with the filtrate flux and device fluid mechanics chosen to minimize fouling and exploit the effects of concentration polarization. Since optimal separation in HPTFF is obtained at a specific filtrate flux, the membrane module should be designed to maintain a nearly uniform flux and transmembrane pressure throughout the module. This can be done using a co-current filtrate flow to balance the feed-side pressure drop through the module. Secondly, the buffer pH and ionic strength are adjusted to maximize differences in the effective volume of the different species. The effective volume of a charged protein (as determined by size exclusion chromatography) accounts for the presence of the diffuse electrical double layer surrounding the protein. Protein transmission through the membrane can be reduced by increasing the effective protein volume, e.g. by increasing the net protein charge (by adjusting the pH) or by increasing the double-layer thickness (by reducing the solution ionic strength). Thirdly, the electrical charge of the membrane is chosen to increase the electrostatic exclusion of all species with like charge. Thus, a positively charged membrane will provide much greater rejection of a positively charged protein than will a negatively charged membrane of the same pore size. Fourthly, protein separations in HPTFF are accomplished using a diafiltration mode to wash the impurity (or product) out of the retentate. The diafiltration maintains an appropriate protein concentration in the retentate throughout the separation, and it allows one to obtain purification factors for products collected in the retentate that are much greater than the membrane selectivity due to the continual removal of impurities in the filtrate.

Although HPTFF is still a new membrane technology, a number of recent studies have clearly demonstrated the potential of this separation technique. Several of these results are summarized in **Table 2**. Purification factors for the separation of bovine serum albumin (BSA) from an antigen-binding fragment (Fab) were greater than 800-fold with either protein collected in the retentate depending upon the choice of solution pH and membrane surface charge. BSA and haemoglobin have essentially identical molecular weight but different surface charge characteristics. In this case, operation at pH 7 caused a strong electrostatic exclusion of the negatively charged BSA from the negatively charged membrane. The separation of BSA monomer and dimer occurs primarily because of the difference in protein size, with the

Table 2 Purification factors and yields for HPTFF processes[a]

Product (MW)	*Impurity (MW)*	*Purification factor*	*Yield*
BSA (68 000)	Fab (45 000)	990	94%
Fab (45 000)	BSA (68 000)	830	69%
BSA (68 000)	Hb (67 000)	100	68%
IgG (155 000)	BSA (69 000)	30	84%
BSA (68 000)	BSA dimer (136 000)	9	86%

[a]BSA, Bovine serum albumin; Fab, antigen-binding fragment from recombinant DNA antibody; Hb, bovine haemoglobin; IgG, human immunoglobin.

smaller monomer collected in the filtrate. However, electrostatic interactions are also important in this system due to the combined effects of size and charge on protein transmission and to possible differences in the charge–pH profiles for the monomer and dimer.

Validation and Integrity Testing

Membrane systems used in bioprocessing applications need to be validated to demonstrate consistent purification and yield with minimal alteration in the properties of the product. Food and Drug Administration regulations provide specific guidelines for validation of sterile filters and virus removal membranes. Validation should always be performed at the same pH, ionic strength and chemical environment as used in the actual process to ensure equivalent physical and chemical characteristics of the product and impurities. Viral clearance studies are typically performed by spiking high titre infectious viruses (with different physical characteristics) into scaled-down production systems.

Integrity testing is critical for all sterile and viral filters to ensure that the system operates at the required level of performance. Integrity tests should be performed both prior to, and immediately after, the actual process wherever possible. Integrity tests performed prior to filtration must not affect the sterility of the connections downstream of the filter. The real test for the sterile filter would be to challenge with *B. diminuta*, but the filter could not be used after this test. Thus, a number of surrogate nondestructive integrity tests have been developed. The industry standards are forward flow, pressure decay and bubble point. Each of these tests is based on the displacement of a fluid from the pores by a second fluid (or gas), with the rate of displacement providing a measure of the membrane pore size characteristics. The gas or intrusion liquid expels the wetting liquid out of the pore when the feed pressure exceeds the capillary force within the pore. The bubble point is defined as the pressure at which the pore is first intruded by the gas. The bubble point for sterilizing grade filters can be correlated to the LRV of *B. diminuta*. Filters with water bubble points of 55 psi or greater typically yield the necessary LRV to be qualified as sterilizing-grade filters. In the forward flow test, one measures the total gas flow rate through the wetted membrane at a fixed pressure. High flow rates indicate the presence of pressure-driven flow through gas-intruded (large) pores. The pressure decay test is performed in a similar fashion, with the gas flow calculated from the rate of pressure decay. A variety of automated integrity test instruments have been developed by the different membrane manufacturers.

Bubble point tests with water-wetted membranes cannot be used to verify virus filter performance since the bubble points for these small pore size membranes would exceed the membrane pressure limits. Air diffusion and bubble point tests can be performed on these membranes using wetting fluids having lower surface tension (e.g. isopropyl alcohol). Liquid intrusion tests using two immiscible fluids (e.g. solutions of a sulfate salt and polyethyleneglycol) have been developed as integrity tests for virus filters and HPTFF membranes.

Summary

Membrane processes should continue to be of critical importance in bioprocessing applications, facilitating the cost-effective production of a wide range of biological products. Ultrafiltration has become the primary means for protein concentration and buffer exchange in the production of therapeutic proteins and industrial enzymes. Sterile filtration is used throughout the bioprocessing industry, and viral filtration is of growing importance in the production of blood products and therapeutic recombinant proteins.

The future is likely to see the continued development of high performance tangential flow filtration as a viable alternative to existing separation technologies for protein purification. There is also growing interest in the development of membrane systems for the preparation of enantiomerically enriched antibiotics, nutraceuticals and pharmaceuticals. These membrane systems use chiral ligands to separate racemic mixtures or they employ immobilized enzymes for direct production of single enantiomers in membrane reactors. Affinity membrane systems are also being actively pursued as alternatives to standard chromatographic resins for a range of adsorptive bioseparations. In this case, the membrane provides an attractive high surface area support with minimal diffusional mass transfer resistance. New advances in membrane materials, modules and processes

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should lead to continued development of membrane systems for bioseparations.

See also: **II / Membrane Separations:** Microfiltration; Ultrafiltration.

Further Reading

Belfort G, Davis RH and Zydney AL (1994) The behavior of suspensions and macromolecular solutions in cross-flow microfiltration. *Journal of Membrane Science* 96: 1.

Blatt WF, Dravid A, Michaels AS and Nelsen L (1970) Solute polarization and cake formation in membrane ultrafiltration. Causes, consequences, and control techniques. In: Flinn JE (ed.) *Membrane Science and Technology*, pp. 47–97. New York: Plenum Press.

Cheryan M (1997) *Ultrafiltration and Microfiltration Handbook*. Lancaster, PA: Technomic.

Ferry JD (1936) Ultrafilter membranes and ultrafiltration. *Chemical Reviews* 18: 373.

Ho WSW and Sirkar KK (eds) (1992) *Membrane Handbook*. New York: Chapman & Hall.

Lonsdale HK (1982) The growth of membrane technology. *Journal of Membrane Science* 10: 81.

McGregor WC (ed.) (1986) *Membrane Separations in Biotechnology*. New York: Marcel Dekker.

van Reis R and Zydney AL (1999) Protein ultrafiltration. In: Flickinger MC and Drew SW (eds) *Encyclopedia of Bioprocess Technology: Fermentation, Biocatalysis, and Bioseparation*, pp. 2197–2214. New York: John Wiley.

Zeman LJ and Zydney AL (1996) *Microfiltration and Ultrafiltration: Principles and Applications*. New York: Marcel Dekker.

Membrane Preparation

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Background

A membrane (Latin, *membrana*, skin) is a thin barrier that permits selective mass transport. Between 1850 and 1900, membranes were used to derive basic physical principles for gas and liquid transport across a barrier material (see the work of Mitchell, Fick and Graham). In these early studies it was already recognized that membranes could be used to separate fluid mixtures. Membranes used at that time included dense films of nitrocellulose, natural rubber, and palladium. The first commercial synthetic membranes were developed by Bachmann and Zsigmondy in the early 1920s in Germany. These microporous nitrocellulose membranes were used for laboratory purposes as well as for the fast detection of bacteria in drinking water. However, until the early 1960s, membranes were not used in any industrial separation process. The major event that ultimately resulted in the widespread use of membranes for separations was the development of integrally-skinned, asymmetric cellulose acetate membranes for water desalination, by Loeb and Sourirajan at UCLA from 1958 to 1960. During a time span of only 10 years, a wide variety of membranes was developed for reverse osmosis, ultrafiltration and microfiltration applications based on modifications of the original membrane preparation method employed by Loeb and Sourirajan. Further-

Table 1 Major milestones in the development of membranes for industrial separations

Period of years	*Advances*
1900–1920	Development of first ultrafiltration and microfiltration membranes made from nitrocellulose (Bechhold, Zsigmondy, Bachmann).
1920–1940	Empirical studies on formation of phase inversion membranes (Bjerrum, Manegold, Elford). Development of cellulose acetate ultrafiltration membranes (Dobry, Duclaux).
1940–1960	Development of integrally-skinned asymmetric cellulose acetate membranes for water desalination by reverse osmosis (Loeb and Sourirajan).
1960–1970	Commercialization of reverse osmosis, ultrafiltration, microfiltration, and dialysis membranes.
1970–1980	Development of thin-film composite membranes made by interfacial polymerization (Cadotte, Riley). Cellulose acetate gas separation membranes (Schell).
1980–1990	Commercialization of gas separation and pervaporation membranes (Henis and Tripodi, Tusel, Brüschke).
1990–2000	Development of inorganic membranes for gas separation and pervaporation.
The next millennium	Commercialization of inorganic membranes.